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10/560,332	09/08/2006	Graeme Semple	22578-004US1 059.US2.PCT	9629

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EXAMINER	
CHU, YONG LIANG	
ART UNIT	PAPER NUMBER
1626	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,332	SEMPLE ET AL.	
	Examiner	Art Unit	
	YONG CHU	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,152-170 and 172-187* is/are pending in the application.

4a) Of the above claim(s) *165, and 179-187* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,152-164,166-170 and 172-178* is/are rejected.

7)☒ Claim(s) *166 and 177* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/22/2007 and 01/17/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 152-170, and 172-187 are pending in the instant application.

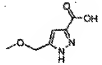
Information Disclosure Statement

Applicants' Information Disclosure Statements, filed on 02/22/2007 and 01/17/2008, have been considered. Please refer to Applicant's copies of the PTO-1449 submitted herewith.

Priority

This application is a 371 of PCT/US04/18389 filed on 06/10/2004, and claims the benefit of U.S. Provisional Patent Application 60/478,664 filed on 06/13/2003.

Response to Lack of Unity

Applicants' election with traverse of Group X (claims 1, 3, 151-167, and 170-178) and elected species of compound 63  on page 53 of the specification in the reply filed on 13/12/2007 is acknowledged. Applicant's arguments regarding unity of invention of the instant inventions have been fully considered, but are not found persuasive. As cited in the previous Office action, the core structure of the instantly claimed compounds lacks unity of invention over prior art teaching based on the primary STN search results, and the instantly cited prior arts. The claims of method of use of

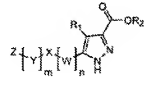
the compounds will not be joined with the product claims of Group X until the product claims become allowable.

Status of the Claims

Claims 179-187 are withdrawn from further consideration by the Examiner as being drawn to non-elected inventions under 37 CFR 1.142(b) due to the restriction requirement dated on 06/14/2007.

Elected and Examined Subject Matter

The scope of the invention of the elected subject matter and the examined subject matter is as follows:

Compounds of Formula (I)  , wherein:

X is –O-, -S-, -S(O)-, or $-S(O)_2-$; and the remaining substituents as defined in claim 1, or a pharmaceutically acceptable salt, solvate or hydrate, or a pharmaceutical composition comprising the said compound in claim 1.

As a result of the election and the corresponding scope of the invention identified supra, claims 165, the remaining subject matter of claims 1, 152-164, 166-170, and 172-178 are further withdrawn from further consideration pursuant to 37 CFR 1.142 (b) as being drawn to non-elected inventions. The withdrawn compounds contain varying functional groups which are chemically recognized to differ in structure, function, and reactivity, and therefore they are patentably distinct from the elected subject matter. Accordingly, claims 1, 152-164, 166-170, and 172-178 will be examined on the merits.

Specification

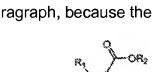
The first paragraph of the specification does not contain all continuing data to which the instant specification claims benefit from (i.e. 371 PCT application date). An appropriate amendment is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 152-164, 166-170, and 172-178 are rejected under 35 U.S.C. 112, first paragraph, because the specification although enabling for the compounds of Formula

(I)  , wherein:

W is an unsubstituted straight or branched chain $C_{1\text{-}5}$alkylene group, **Y** is a straight or branched unsubstituted chain $C_{1\text{-}5}$alkylene group; **X** is –O-, -S-, -S(O)-, or $–S(O)_2$-; $\mathbf{R_1}$ is H or $C_{1\text{-}4}$alkyl; $\mathbf{R_2}$ is H or $C_{1\text{-}8}$alkyl; and **m** and **n** are each 1; or a pharmaceutically acceptable salt, or a composition comprising the said compound in claim 1, does not enable the rest of the claimed subject matter without undue amount experimentation for the reason described below.

As stated in MPEP 2164.01(a), "there are many factors to be considered when determing whether there is sufficient evidence to support a determination that a

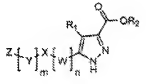
disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The eight Wands factors are applied to claims 1, 152-164, 166-170, and 172-178 of the present invention below:

The Nature of the Invention

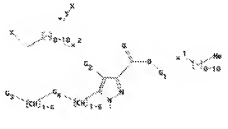
The nature of the invention is a compound of Formula (I)  ,

wherein:

X is –O-, -S-, -S(O)-, or $-S(O)_2-$; and the remaining substituents as defined in claim 1, or a pharmaceutically acceptable salt, solvate or hydrate, or a pharmaceutical composition comprising the said compound in claim 1. These compounds are claimed to be useful for treating a metabolic-related disorder.

The State of the Prior Art

According to STN Chemical Structure database search on the claimed



compounds of the scope

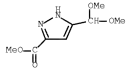
G1:H,[*1]

G2:H,X,[*1],[*2],[*3]

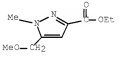
G3:H,X,Cy

G4:O,S

, no reference has been disclosed on how to use the compounds of Formula (I) for pharmaceutical application, except a couple of references,



which disclosed compound (CAS RN 75436-38-3) by Stanovnik et al., *Science of Synthesis, 2002, Vol. 12,* pp. 15-225, with publication date May, 2002, and compound (CAS RN 199480-31-4, Example 66 at paragraph[365])



. These compounds are used as chemical intermediates, but not as pharmaceuticals.

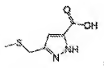
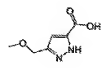
The level of skill in the art

The level of skill in the art (pharmaceutical and medicinal chemists, and physicians) would be high.

The predictability or lack thereof in the art

As demonstrated earlier, most of the compounds claimed in the instant application, do not exist at the time of the original filing of the instant application, which renders the prior art unpredictable for making or using products for pharmaceutical applications as claimed on such a ground scale. Because of high level of unpredictability associated with these compounds or composition for its functionality for treating metabolic disorder, a greater amount of evidentiary support is needed to fully satisfy the requirement of 35 U.S.C 112, first paragraph. It is noted that pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance presented (by the inventor)

The specification in the present invention discloses the biological activity of agonists to hRUP25 (RUP25 (EC_{50})) for only two compounds (i.e. compound 48  , and compound 63 ), wherein **W** is an unsubstituted

straight or branched chain C_{1-5}alkylene group, **Y** is a straight or branched unsubstituted chain C_{1-5}alkylene group; **X** is –O-, or -S-; $\mathbf{R_1}$ is H or C_{1-4}alkyl; $\mathbf{R_2}$ is H or C_{1-8}alkyl; and **m** and **n** are each 1, but not the other compounds as been currently examined.

The presence or absence of working examples

As noted in the section above, the specification discloses the general role of the compounds of 1, 152-164, 166-170, and 172-178. However, the specification has no working examples of where the core compound is anything but the compounds 48 and 63. A single embodiment may provide broad enablement in case involving predictable factors, but more is required in cases involving unpredictable factors, such as pharmaceuticals.

The quantity of experimentation needed (to make and/or use the invention)

Given the very limit direction or guidance (with only two working examples) in the specification for any of the extremely large number of compounds that would be encompassed by the descriptions, it would cause a skilled artisan an undue amount of experimentation to determine which product the process of using was describing. Applicant may overcome this rejection by deleting the non-enabled subject matter or pointing out where in the specification support for the additional compounds can be found.

Therefore, claims 1, 152-164, 166-170, and 172-178 are rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 152-164, 166-170, and 172-178 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 1, 152-164, 166-170, and 172-178 are rejected due to claiming a solvate or hydrate of a compound of Formula (I). The instant specification does not define the terms "solvate" and "hydrate". According to Vippagunta et al., *Advanced Drug Delivery Reviews*, page 1, a solvate and hydrate exist as crystalline forms. They are specific crystalline forms of a compound that can crystallize in different forms, and not all compounds can form crystalline. The specification does not reasonably provide enablement for forming crystalline of each of the compound list in the claims. Because of high level of unpredictability associated with crystalline of the compounds, a greater amount of evidentiary support is needed to fully satisfy the requirement of 35 U.S.C 112, first paragraph. It is noted that crystallization art is unpredictable, requiring each embodiment to be individually assessed for the possibility.

A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that compounds fall within the scope of a claim will posses the crystalline form of the compound. To practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which compounds would form crystalline, with no assurance of success.

Claims 1, 152-164, 166-170, and 172-178 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. According to Vippagunta et al., *Advanced Drug Delivery Reviews*, page 1, a "solvate" and "hydrate" exist as crystalline forms, which are packed in a regularly ordered, repeating pattern extending in all three spatial dimensions. However, such "solvate" and "hydrate" are not described in the specification to reasonably convey one skilled in the art. There is not even a single example of crystal form of solvate or hydrate disclosed in the Specification. Therefore, the specification fails to comply with the written description requirement.

Double Patenting

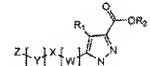
The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

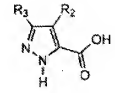
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 152-164, 166-170, and 172-178 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 5-14, 20-28, and 30 of copending Application No. 10/530,902 ("the `902 application"). Although the conflicting claims are not identical, they are not patentably distinct from each other because the description as follows:

Applicants' claims relate to a compound of Formula (Ia)  , wherein:

X is –O-, -S-, -S(O)-, or $-S(O)_2-$; and the remaining substituents as defined in claim 1, or a pharmaceutically acceptable salt, solvate or hydrate, or a pharmaceutical composition comprising the said compound in claim 1.

Determination of the scope and content of the prior art (MPEP §2141.01)



The `902 application claims a compound of formula (Ia)

wherein:

R_2 is H, halogen, C_{1-12} alkyl or C_{1-12} haloalkyl; and

R_3 is C_{3-6} cycloalkyl, C_{1-12} alkyl, C_{1-12} haloalkyl, C_{3-6} cycloalkyl-C_{1-4}-alkylene, aryl-C_{1-4}-alkylene or heteroaryl-C_{1-4}-alkylene, wherein said aryl-C_{1-4}-alkylene and heteroaryl-C_{1-4}-alkylene can be optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-4} acyl, C_{1-4} acyloxy, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} alkyl, C_{1-4} alkylcarboxamide, C_{2-4} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, C_{1-4} alkylamino, C_{1-4} dialkylamino, arylsulfonyl, carbo-C_{1-4}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{1-4} dialkylcarboxamide, C_{1-4} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclyl, hydroxyl, thio, nitro, C_{3-6} oxo-cycloalkyl, sulfonamide and sulfonic acid; or

a pharmaceutically acceptable salt, solvate or hydrate thereof;

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the `902 application and the instantly claimed compound, is that the chain at C-5 position is alkyl group (i.e. butyl, see compound 8, Example 5.8) for the `902 application, and could be alkoxyl for the instant application.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

To those skilled in the medicinal chemical art, one compound with alkyl is not such an advance over alkoxyl-type compounds as required invention because they are structurally so similar, and for one skilled in the art, knowing properties of one member of series would in general know what to expect in adjacent members, especially they have the same utility as a pharmaceutical compound or composition, unless there are unique prosperities contribute from this variations (or unexpected results).

Claim Objections

Claim 166 is objected to for containing elected and non-elected subject matter. The elected subject matter has been identified supra.

Claim 178 is objected to for inappropriate Markush-type claim. More specifically, at page 3 of claim 177 5-Ethoxymethyl-1H-pyrazole-3-carboxylic acid; or 5-(2,2-Diethoxy-ethyl)-1H-pyrazole-3-carboxylic acid; , it should be "and" not "or" after "the group consisting of:". Appropriate correction is required.

Conclusion

- Claims 166 and 177 are objected.
- Claims 1, 152-164, 166-170, and 172-178 are rejected.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Chu whose telephone number is 571-272-5759. The examiner can normally be reached between 7:00 am - 3:30 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Supervisory Patent Examiner
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